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基于中西医临床病症特点的眩晕动物模型分析

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【摘要】 目的 基于眩晕的中西医临床病症特点,对其现有动物模型进行分类分析,评估模型的临床吻合情况及其优缺点,以期改进现有的动物模型、为临床研究提供更直观的参考。方法 检索数据库中从 2000 年 1 月~2023 年 3 月的眩晕动物模型资料,根据造模方法进行分类、结合眩晕的中西医临床病症特点和现有的动物模型评价方法,对各模型进行赋值,评估其临床吻合情况、评价模型优缺点。结果 现有的眩晕动物模型有颈部手术模型、运动刺激模型、耳源性刺激模型、硬化剂注射模型、飞行变压模型、椎动脉结扎模型、瘀血注射模型;其中,西医吻合度较高的是颈部手术模型(65%)、耳源刺激模型(65%),所有模型中医吻合度均中等(50% ≤ 吻合度 < 60%)或较低(吻合度 < 50%),没有中、西医吻合度同时较高的模型。结论 目前眩晕动物模型以西医疾病模型为主,缺乏中医证型模型,中、西医临床吻合度均较高的模型较少,未能突出中医药辨证论治的特色。因此,构建出与中西医临床病症特点紧密结合的眩晕动物模型,可为抗眩晕新药的研发、筛选、临床评价提供更合理更全面的实验支撑。

【关键词】 眩晕;临床病症;动物模型
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Analysis of animal models of vertigo based on the characteristics of clinical conditions in Chinese and Western medicines

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【**Abstract**】 **Objective** To classify and analyze the existing animal models of vertigo based on the clinical characteristics of Chinese and Western medicines, evaluate the clinical fit of the models, and their advantages and disadvantages, to improve the existing animal models and provide a more intuitive reference for clinical research. **Methods** The existing animal models of vertigo in the database from January 2000 to March 2023 were searched, and the models were classified by the modeling method combined with the characteristics of Chinese and Western medicine clinical conditions of vertigo and the existing animal model evaluation method, and assigned values to evaluate the clinical fit and the advantages and disadvantages of the models. **Results** The existing animal models of vertigo were neck surgery, motor stimulation, otogenic stimulation, sclerotherapy injection, flight variation pressure, vertebral artery ligation, and stasis injection models. Among them, the Western medical fit was high for the neck surgery model (65%) and otogenic stimulation model

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(65%). All models had a moderate Chinese medical fit (50% ≤ fit < 60%) or low(fit < 50%) TCM anast omosis. No model had both high Chinese and Western medicines anastomosis. **Conclusions** The animal models of vertigo are mainly Western medicine disease models, Chinese medicine evidence models are lacking, and few models have a high clinical fit between Chinese and Western medicines, which fail to highlight the characteristics of Chinese medicine. Therefore, the establishment of animal models of vertigo that are closely integrated with the clinical characteristics of Chinese and Western medicines may provide more reasonable and comprehensive experimental support for the development, screening, and clinical evaluation of new anti-vertigo drugs.

【**Keywords**】 vertigo; clinical conditions; animal models

Conflicts of Interest: The authors declare no conflict of interest.

眩晕(vertigo)是一种运动性或位置性错觉,是由前庭神经系统疾病引起机体平衡功能障碍和对空间定位障碍所导致的[1]。一般表现是感觉自身或外部物体在某一方向上的突然旋转、漂浮、漂移或滚动[2]。在现代医学中,眩晕只是一种症状,但病因复杂,梅尼埃病、椎基底动脉供血不足、颈椎病是最常见的病因[3],且分为周围性眩晕和中枢性眩晕[4],其中,周围性眩晕占 30% ~ 50%,中枢性眩晕占 20% ~ 30%,综合内科学疾病占 10% ~ 25%,还有 15% ~ 25%眩晕的原因尚不明确[5]。周围性眩晕对受体位置的影响较大,症状相对较重,急性迷路炎、耳石症、梅尼埃病、前庭神经炎和其他疾病的患者常会出现听力障碍等其他并发症[6];中枢性眩晕影响受体位置因素较少,以及伴有动脉粥样硬化和脑血管痉挛的脑血管疾病患者则因相应脑组织缺氧和缺血而头晕目眩[2]。中医认为,眩晕病位在脑,疾病性质为“虚实夹杂、本虚标实”,虚证多是肝、脾、肾三个脏器的虚损[7-8],实证多是风、火、痰、瘀为患引起[9],其中医基本病机(即发生、发展与变化的机理)是清窍失养[10]。《黄帝内经》中称其为“眩”“眩扑”“脑转”等;宋代严用和在《严氏济生方·眩晕门》第一次命名为眩晕,并给眩晕下定义:所谓眩晕者,眼花屋转,起则眩倒是也[11]。中医临床主要分肝阳上亢、肝火上炎、痰浊上蒙、瘀血阻窍、气血亏虚、肝肾阴虚六个证型。眩晕是涉及神经与耳鼻喉的复杂综合症状,还涉及内科、骨科和其他学科的各种临床表现,临床诊断比较困难[12],在临床问诊中易与头晕混淆,眩晕是指视线的旋转或闭目发黑,头晕是感觉到自己或外部景物的旋转,而二者常同时出现。目前国内外临床数据发现西医治疗效果欠佳,中医辨证论治有潜在优势[13],但在临床观察中多为小样本试验或个案举例,存在缺乏统一的疗效评定标准,因而建立科学的大样本的实验动物,寻找可行的观察指标,对眩晕的临床治疗药物的研发意义重大[13],因此,本研究旨在分析各模型与中西医临床的符合程度及优缺点,以期建立更规范的中西医病证结合动物模型,为其相关研究提供实验支撑,促进临床治疗[14]。

1　材料与方法

1.1　文献来源

以“眩晕”和“动物模型”为主题,在中国知网、维普、万方和中国生物医学数据库进行检索[15];以“vertigo”“motion sickness”“laboratory animal model”“models animal”“experimental animal model”“animal model”为关键词,在 Web of Science、PubMed、Embase、Cochrane Library 数据库进行检索,收集从 2000 年 1 月 ~ 2023 年 3 月内有关“眩晕动物”的文献。

1.2　文献纳入、排除标准

1.2.1　纳入标准

(1)关于眩晕动物模型的实验性文献;(2)造模刺激因子和方法等信息完整的文献[16]。

1.2.2　排除标准

(1)剔除科技成果、会议论文、综述类型、临床试验的文献;(2)剔除无法获取全文的文献;(3)剔除重复文献。

1.3　评价方法

依据公认最新的中、西医临床病症诊断标准,并将前者细分为Ⅰ、Ⅱ类指标(主证和次证),后者分为Ⅰ、Ⅱ级指标(核心、相关指标),参照综合权重法进行各自量化积分,依据积分结果与临床病症进行吻合,依此进行模型评价[17]。

1.3.1　眩晕的西医诊断标准

根据 2021 年发布的《眩晕急诊诊断与治疗指南》[18]、2019 年发布的《眩晕急诊诊断与治疗专家共识》[19]和 2021 年发布的《老年人头晕/眩晕诊疗多学科专家共识》[20],总结出西医眩晕诊断标准。

眩晕的程度大致有三个级别[21-22]:一级头下沉仍能自持;二级闭眼睛静卧则不晕,但运动则感觉自身或环境在旋转;三级比较严重,闭目静卧有旋转感觉。评价标准:符合任一项核心指标(Ⅰ)积分 10%,符合任一项相关指标(Ⅱ)积分 5%,总分 100%[23],见表 1。

表 1 西医诊断标准

Table 1 Diagnostic criteria of Western medicine

指标 Indicators	表现 Performance
Ⅰ临床表现(核心指标) Ⅰ clinical performance (core indicators)	①摇头;②两眼倾斜;③眼球震颤;④耳鸣;⑤听力下降;⑥口角及四肢麻木。 ①Shaking head. ②Tilting eyes. ③Nystagmus. ④Ninnitus. ⑤Hearing loss. ⑥Numbness at the corners of the mouth and extremities.
Ⅱ临床检查(相关指标) Ⅱ clinical examination (relevant indicators)	①血压检查;②心电图、心率检查;③脑神经检查;④运动感觉及反射;⑤头脉冲试验;⑥步态及平衡检查;⑦颈椎检查;⑧头颅影像学佐证(MRI、CT、B 超)。 ①Blood pressure examination. ②Electrocardiogram, heart rate examination. ③Brain nerve examination. ④Motor sensation and reflex. ⑤Head pulse test. ⑥Gait and balance examination. ⑦Cervical spine examination. ⑧Cranial imaging corroboration (MRI, CT, B-mode ultrasound).

1.3.2 眩晕中医辩证分型及临床症状

参照 2017 年发布的《眩晕诊治多学科专家共识》[24]和眩晕的诊断依据、证侯分类、疗效评定—中华人民共和国中医药行业标准《中医内科病证诊断疗效标准》(ZY/T001.1-94)(2022 年)[25],眩晕的中医辩证主症主要有:①头目眩晕;②视线旋转;③轻者闭眼睛;④严重者像晕船,甚至摔倒。次要症状:①恶心、呕吐;②眼球颤动;③耳鸣、耳聋;④出汗;⑤面色发白等;每项主症赋值 15%,每项次证赋值 8%,总分 100%。中医将眩晕辩为 6 个证型,见表 2。

表 2 中医辩证标准

Table 2 Dialectical standard of traditional Chinese medicine

类型 Types	主证 Main certificate	次证 Secondary symptom
肝阳上亢 Hyperactive of liver-yang	眩晕耳鸣,头痛且胀。 Vertigo, tinnitus, have a headache and be bloated.	遇劳恼怒加重,肢麻震颤,失眠多梦,急躁易怒。 Aggravated by exertion and anger, paresthesia and tremor, sleeplessness and nightmares, irritable.
肝火上炎 Liver fire fiaming	头晕且痛。 Dizzy and aching.	目赤口苦,胸胁胀痛,烦躁易怒,寐少多梦,小便黄,大便干结。 Watery eyes and bitter mouth, chest and hypochondrium, irritable, sleeplessness and dreaminess, yellow urine and dry stools.
痰浊上蒙[26] Obstructed by phlegm[26]	眩晕,头重如蒙。 Dizziness, have a heavy head as if blinded.	视物旋转,胸闷作恶,呕吐痰涎,食少多寐[27]。 Parallax, chest tightneschest tightness as idiom, vomiting and salivation, little food and much sleep[27].
瘀血阻窍 Stasis of blood clogging the orifices	眩晕头痛,健忘。 Dizziness and headache, forgetful.	失眠,心悸,精神不振,耳鸣耳聋,面唇紫暗。 Insomnia, palpitations, mental discomfort, tinnitus and deafness, purple and dark facial lips.
气血亏虚[28] Deficiency of qi and blood[28]	头晕目眩,动则加剧,遇劳则发。 Dizziness, aggravate by slow motion, break out in the morning when one is working.	面色觥白,爪甲不荣,神疲乏力,心悸少寐,纳差食少,便溏。 White face, unglamorous claws and nails, fatigue, palpitations and sleeplessness, poor appetite, loose stools.
肝肾阴虚 Deficiency of liver and kidney yin	眩晕久发不已,视力减退,两目干涩。 Have prolonged vertigo, hyperopia, dryness in both eyes.	少寐健忘,心烦口干,耳鸣,神疲乏力,腰酸膝软,遗精。 Hypersomnia and forgetfulness, irritability and dry mouth, tinnitus, fatigue, lumbago and weakness, seminal emission.

2 结果

2.1 眩晕模型动物

共纳入有效文献 131 篇,目前研究眩晕多以大鼠、小鼠、家兔、豚鼠等为建模对象[29],且多选择 SD 大鼠和 KM 小鼠,因其容易获得、价格经济;其中,手术建模常用大鼠,但术后护理难且手术精度不易把控[30],易死于术后感染;小鼠的耐受力比大鼠弱,不适合长期造模和给药;家兔、豚鼠等受建模成本高、不宜多样本复制等限制。因此需根据实验需求和预期结果选择合适的模型动物[14]。

2.2 眩晕动物模型

目前眩晕动物实验造模方法主要有手术法、刺激法、注射法等[14],具体模型与临床吻合度及模型优缺点分析[31],见表 3。

表 3 结果显示,各动物模型吻合度高低不一,高低的分级标准为:吻合度高吻合度:西医 ≥ 60%,中医 ≥ 60%;中吻合度:50% ≤ 西医 < 60%,50% ≤ 中医 < 60%;低吻合度:西医 < 50%,中医 < 50%[41]。

表 3　眩晕动物模型分析

Table 3　Analysis of vertigo animal model

模型分类 Model classification	实验动物 Experimental animals	造模方法 Moulding method	与临床病症特点的吻合度 Consistency with clinical disease characteristics	模型优缺点 Model advantages and disadvantages
颈部手术模型[32] Neck surgery method[32]	SPF 级 SD 雄性大鼠 SPF-grade SD male rats	切断颈部后方的肌肉组织，并去除颈椎的第五和第六棘突和韧带，破坏颈椎的第五和第六关节囊。 Musculature at the back of the neck is cut and the fifth and sixth spinous processes and ligaments of the cervical spine are removed, disrupting the fifth and sixth joint capsules of the cervical spine.	符合西医指标Ⅰ①②③④⑤、Ⅱ①②③，吻合度 65%；中医主证①②、次证①，吻合度 38%。 Western medicine index Ⅰ①②③④⑤、Ⅱ①②③, 65% match; TCM primary evidence ①②, secondary evidence ①, 38% match.	优点：方法经典； 缺点：手术操作难度大。 Advantages: Classic approach; Disadvantages: Difficult surgical operation.
运动刺激模型 Exercise stimulation method	KM 小鼠 KM mice	在旋转设备中，不受约束，水平轴顺时针、逆时针方向交替变速旋转刺激，持续刺激 30 min。 In the rotating device, unconstrained, the horizontal axis was rotated in alternating clockwise and counterclockwise directions with variable speed for 30 min of continuous stimulation.	符合西医指标Ⅰ①②③、Ⅱ①②③，吻合度 45%； 中医：主证①②、次证①④，吻合度 46%。 Western medicine index Ⅰ①②③、Ⅱ①②③, 45% match; TCM primary evidence ①②, secondary evidence ①④, 46% match.	优点：操作简单，价格低廉，重复性高，成功率高； 缺点：受潜伏期影响，眩晕持续时间存在偏差。 Advantages: Simple operation, low price, high repeatability and high success rate; Disadvantages: Affected by the latency period, there is a deviation in the duration of vertigo.
耳源性刺激模型 Otogenic stimulation method	豚鼠 Cavia porcellus	头部倾斜并固定，水平半圆形管处在垂直位置，取 1 mL 冰水将其推入外耳道。 Head is tilted and held in place with the horizontal semicircular tube in a vertical position and 1 mL of ice water is taken and pushed into the external auditory canal.	符合西医指标Ⅰ①②③④⑤、Ⅱ①②③，吻合度 65%；中医：主证①②、次证①④⑤，吻合度 54%。 Western medicine index Ⅰ①②③④⑤, Ⅱ①②③, 65% match; TCM primary evidence ①②, secondary evidence ①④⑤, 54% match.	优点：操作简单，原理明确可靠，周期可控； 缺点：豚鼠饲养难度高，易死亡。 Advantages: Simple operation, clear and reliable principle, controllable cycle time; Disadvantages: High difficulty in raising guinea pigs, easy to die.
硬化剂注射模型[33] Sclerotherapy injection method[33]	日本大耳兔[34]、新西兰家兔 Japanese big eared rabbit[34], New Zealand Domestic rabbit	每天在颈椎横突旁的软组织中注射 10 mL 的 5%硬化剂（油酸甘氨酸），每周重复 1 次。 10 mL of 5% sclerosing agent (glycine oleate) was injected daily into the soft tissue adjacent to the transverse processes of the cervical spine and repeated once a week.	符合西医指标Ⅰ①②③④、Ⅱ①②③，吻合度 55%；中医：主证①②、次证①②，吻合度 46%。 Western medicine index Ⅰ①②③④、Ⅱ①②③, 55% match; TCM primary evidence ①②, secondary evidence ①②, 46% match.	优点：安全可靠，操作方便，注射快捷，贴合临床； 缺点：造模周期较长。 Advantages: Safe, reliable, easy to operate, quick to inject and clinically relevant; Disadvantage: Longer mold-making period.
飞行变压模型[35] Flying variable pressure method[35]	小鼠 Mice	在低压的条件下，单次或多次震荡头部导致耳囊内的耳蜗脱离[36]。 Single or multiple shocks to the head under low pressure conditions resulting in detachment of the cochlea in the ear sac[36].	符合西医指标Ⅰ①②③、Ⅱ①②③，吻合度 45%；中医：主证①②、次证①③，吻合度 46%。 Western medicine index Ⅰ①②③, Ⅱ①②③, 45% match; TCM primary evidence ①②, secondary evidence ①③, 46% match.	优点：操作难度小，重复性高； 缺点：中耳相对高压易损伤听功能。 Advantages: Low operational difficulty and high repeatability; Disadvantages: Relatively high pressure in the middle ear can easily damage hearing function.
椎动脉结扎模型[37] Vertebral artery ligation[37]	家兔 Domestic rabbit	在用 25%氨基甲酸乙酯进行静脉麻醉后，将皮肤从颈部中间切至第一肋骨的上边缘。分开气管后，进行气管的插管，并沿右侧的锁骨下动脉能发现右侧的颈椎动脉然后结扎[38]。 After intravenous anesthesia with 25% urethane, the skin was cut from the middle of the neck to the upper edge of the first rib. After separation of the trachea, intubation of the trachea was performed and the right cervical artery could be found along the right subclavian artery and then ligated[38].	符合西医指标Ⅰ①②③④、Ⅱ①②③，吻合度 55%；中医：主证①②、次证①③⑤，吻合度 54%。 Western medicine index Ⅰ①②③④、Ⅱ①②③, 55% match; TCM primary evidence ①②, secondary evidence①③⑤, 54% match.	优点：操作相对简单、易行； 缺点：未能完全反映椎动脉型眩晕的发病机制。 Advantages: Relatively simple and easy to operate; Disadvantage: It does not fully reflect the pathogenesis of vertebral artery type vertigo.

续表 3

模型分类 Model classification	实验动物 Experimental animals	造模方法 Moulding method	与临床病症特点的吻合度 Consistency with clinical disease characteristics	模型优缺点 Model advantages and disadvantages
瘀血注射模型[39] Blood stasis blocking method[39]	日本大耳兔[40] Japanese big eared rabbit[40]	从同种异体股动脉中抽取 4 mL 血液，将其与 25% 的生理盐水按 1∶1 混合。再加入 0.1 mL 肝素钠摇匀，加入 1 mL 引物，制作成瘀血备用。在造模的左侧颈椎夹肌，横突间肌，横突棘肌及其肌间间隙注射瘀血（每只 9 mL）。4 mL of blood was drawn from the homologous femoral artery and mixed with 25% of saline at 1∶1. Then 0.1 mL of sodium heparin was added and shaken, and 1 mL of primer was added to make stasis blood for backup. Stasis blood (9 mL each) was injected into the left cervical pinch muscle, transverse interosseous muscle, transverse spinous muscle and its interosseous space in the molded left side.	符合西医指标Ⅰ①②③、Ⅱ①②③，吻合度 45%；中医：主证①②、次证①③，吻合度 46%。Western medicine index Ⅰ①②③, Ⅱ①②③, 45% match; TCM primary evidence ①②, secondary evidence ①③, 46% match.	优点：可操作性强，模型较稳定；缺点：易引起椎颈椎间盘改变。Advantages: High operability and more stable models; Disadvantages: Easy to cause vertebral cervical disc changes.

3 结论与讨论

综上，目前眩晕动物模型以西医疾病模型为主，缺乏中医证型模型，中、西医临床吻合度均较高的模型较少，未能突出中医药辨证论治的特色，至今仍无完全公认的将中西医病证特点结合的眩晕造模方法。

理想的动物模型至少需要满足与人类疾病具有相似的发病机理（疾病同源性）、相似的行为表象（表象一致性）、相似的药物治疗反应（药物预见性）这三个一致性验证。眩晕是多种疾病的伴随症状，目前现有的眩晕动物模型各有局限，就各模型与临床病症吻合情况而言，颈部手术模型，通过颈源性因素影响颈部血流循环，使骨质增生，压迫颈动脉而产生眩晕，动物实验中通过观察动物步态变化，以动物站立、移动障碍，或停滞不前、摇晃、调转方向移动的行为表象来评价造模是否成功[42]，满足与人类疾病同源性、表象一致性，该模型是临床上研究抗缺血性眩晕药物的最常用建模方法；耳源性刺激模型，通过刺激外耳，使神经冲动信号经过前庭神经、前庭核、内侧纵束神经通路作用动物大脑而产生眩晕，具有疾病同源性，是耳源性反复发作眩晕临床研究的首选模型；硬化剂注射模型是通过注射硬化剂损害椎动脉、降低椎动脉血流且破坏颈椎动力平衡，多普勒、病理学结果能证明其更贴近临床上颈部狭窄引起的眩晕；椎动脉结扎模型是通过结扎一侧椎动脉引起椎基底动脉供血不足而造成而制成静力失衡为主的颈性眩晕模型，多普勒和椎动脉造影结果验证模型成功，与临床颈性眩晕具有疾病同源性；运动刺激模型是通过旋转引起前庭植物神经系统反应加强出现眩晕，符合疾病同源性和表象一致性，是临床上研究良性阵发性眩晕的常用模型；飞行变压模型在外界高压情况下，中耳相对于外界的高压，出现几秒至几分钟的急性变压性眩晕，该模型与飞行员由于快速爬升、紧急迫降等引起的眩晕相近，满足急性眩晕的发病机理；瘀血注射模型，是基于中医瘀血阻络理论进行复制，符合眩晕中医瘀血阻窍的证型病机和表现，也是椎动脉型颈椎病模型。各模型与临床病症吻合情况各有侧重，目前的眩晕模型主要以西医致病原因为造模依据，缺少体现中医病症特点的模型。但至今仍无公认的完全成熟的、完全吻合中西医病症的造模方法[43]。各模型各自的基本优缺点由本文分析所示，但存在的主要的共性缺陷是中医相关的检测指标不易把控，例如舌苔脉象难以用于动物模型评判[42]；缺乏与中医病因病机完全匹配的评价指标；体现的中医证候特点不够完整[44]；未重视与人类疾病的药物预见性的验证等。

现有的模型都各有优缺点，在临床吻合程度和优缺点的基础上，可将模型进行相应改进。结合中医致病因素，例如给予高脂饲料喂养来助生体内湿热的同时碍胃伤脾[45]，来助生痰阻血瘀[17]；将中医四诊辩证方法量化应用于模型评价指标中，例如通过观察动物毛发光泽度、精神状态、大便软硬等来评分，来辩体虚证型疾病程度，增加对动物的唇色、舌质、皮肤等改变的记录来进行直观评价；同时，考虑动物模型与人类疾病同源性、表象一致性、药物预见性来建立与中西医临床病症特点紧密结合的

眩晕动物模型,为抗眩晕新药的研发、筛选、临床评价提供更合理更全面的实验支撑[38]。

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胰腺导管腺癌类器官模型的建立及个体化治疗策略的筛选

近年来,胰腺导管腺癌(pancreatic ductal adenocarcinoma,PDAC)的发病率明显上升,且 PDAC 发病隐匿、恶性程度高、化疗反应差异大,导致 5 年相对生存率低。对癌症患者进行个体化针对性的治疗,可以较大程度改善临床患者预后。类器官(patient-derived organoid,PDO)是由干细胞增殖和分化形成的组织或器官样结构,是近年来新兴的体外 3D 培养模型。肿瘤 PDO 模型可以较好地维持原发瘤的组织形态特征。其构建策略是从患者肿瘤组织中提取原代细胞,利用生长因子和基质胶来创建模拟人体内的三维生长环境。类器官能在体外模拟肿瘤细胞的病理状态,比人体临床试验中的药物反应具有更高的相关性,可应用于临床患者的药物筛选,为肿瘤患者的个体化治疗提供了良好的实验平台。此外,通过深度测序或表型分析发现的基因突变和药物治疗靶点,对研究 PDAC 的发病机制和耐药性具有重要意义。在本研究中,作者重点探索了 PDAC 类器官模型的培养条件和构建方法,分析了影响类器官模型成功率的主要因素,同时利用病理分析和 DNA 测序证明了 PDAC 类器官保持了原发肿瘤组织的生物学特征。进一步选择了 4 种临床常用的化疗药物进行单一或联合治疗,分析药物在 PDO 模型中的敏感性,为 PDO 模型广泛应用于胰腺导管癌患者个体化药物筛选提供思路。

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